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Tamoxifen versus Tamoxifen and Ovarian Suppression in Premenopausal Hormone Positive early Breast Cancer (Retrospective study)

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ABSTRACT

Background: breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. The American Cancer Society estimated that 249, 260 Americans were diagnosed with invasive breast cancer and 40, 890 were died of the disease in the United States in 2016.**Aim of the Work:** this was a retrospective study aimed to evaluate the disease free survival, overall survival and toxicity profile in premenopausal breast cancer patient who received tamoxifen versus tamoxifen with ovarian suppression (LHRH) agonists as adjuvant hormonal treatment.**Patients and Methods:** this was a retrospective cohort study. Premenopausal Female patients with Breast Cancer, who received Tamoxifen with or without Ovarian Function Suppression (LHRH agonist for 2 years) as adjuvant hormonal treatment, presented to clinical Oncology Department, Al-Hussein University Hospital in the period between January 2008 and January 2015 in Breast Cancer Unit, Clinical Oncology Department, Al-Hussein University Hospital. **Results:** in our retrospective analysis there was no statistical significant difference in the primary endpoint of DFS between group I who received tamoxifen and group II receiving tamoxifen plus ovarian suppression (2-year DFS, 65.3% vs. 75.0%) with (P value=0.838 not significant).**Conclusion:** we concluded that adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall population of premenopausal women in this study (P=0.15 not significant).

Keywords: tamoxifen, ovarian suppression, premenopausal hormone, breast cancer

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women. The American Cancer Society estimates that 249, 260 Americans were diagnosed with invasive breast cancer and 40, 890 were died of the disease in the United States in 2016 [(1)].Treatment of breast cancer included treatment of local disease with surgery, radiation therapy or both and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies were based on several prognostic and predictive factors. These factors included tumor histology, clinical and pathologic characteristics of the primary tumor, ALN status, tumor hormone receptor (ERlPR) content, tumor HER2 status [(2)].Adjuvant endocrine therapy is an integral component of care for endocrine-dependent breast cancer (EDBC). The goal of this type of therapy is to counteract the production and the action of estrogens [(3)].Adjuvant endocrine therapy with tamoxifen had been recommended for premenopausal women with hormone receptor positive breast cancer during the past 15 years [(4)].The American Society of Clinical Oncology endorsed guidelines recommending that ovarian ablation or suppression not be added routinely to adjuvant therapy in premenopausal women [(5)].International consensus guidelines for breast cancer management in young women suggested that the addition of a gonadotropin-releasing hormone (GnRH) agonist to tamoxifen be discussed on an individualized basis [(6)].

AIM of the WORK

This retrospective study aimed to evaluate the disease free survival, overall survival and toxicity profile in premenopausal breast cancer patient receiving tamoxifen versus tamoxifen with ovarian suppression (LHRH) agonists as adjuvant hormonal treatment.

PATIENTS and METHODS

Type of study:

A retrospective cohort study

Study population:

Premenopausal female patients with breast cancer, who received tamoxifen with or without ovarian function suppression (LHRH

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agonist for 2 years) as adjuvant hormonal treatment, presented to clinical Oncology Department, Al-Hussein University Hospital in the period between January 2008 and January 2015. **The study was approved by the Ethics Board of Al-Azhar University.**

Study setting:

Breast Cancer Unit, Clinical Oncology Department, Al-Hussein University Hospital.

Inclusion criteria

All patients included in this study were female patients with early stage breast cancer and had the following criteria:

- Premenopausal patients.
- Age between (18) and (45) years old.
- Performance status (0 to II) WHO.
- Histopathologically proven of breast carcinoma.
- Tumor that expressed estrogen or progesterone receptors in at least 10% of the cells independent of HER2neu status.
- Stages (Stage I and stage IIA, IIB, stage IIIA)
- Underwent to surgery either (modified radical mastectomy or conservative breast surgery).

Exclusion criteria

Any patient has one of the following criteria will be excluded from the study:

- Any patient who was irregular on treatment or follow up.
- Any file with incomplete data.
- Any patient developed endometrial hyperplasia during the treatment course and shifted to other line of hormonal treatment.
- Any Patient with histopathologically proved ductal carcinoma *in situ* or lobular carcinoma *in situ.*
- Patients with artificial menopause either by surgery or radiotherapy with postmenopausal hormonal level (E2 & FSH).
- Patients with double malignancy except basal cell carcinoma.
- Patients that received neo-adjuvant hormonal treatment.
- Hormone negative breast cancer or unknown hormonal status.
- Patients with inflammatory carcinoma of the breast.
- Patients who developed metastasis during or early after the primary treatment.

Methodology:

The patient's data were extracted and analyzed. The patient, tumor and all prognostic as (age, TNM, surgery, chemotherapy and radiotherapy) data was tabulated and survival data was recorded and tabulated to be presented to SPSS program to analyze the different prognostic criteria and Kaplan-Mier curves were obtained for survival analysis. Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For comparison of age (as numeric variable) between two groups (Tamoxifen versus tamoxifen and LHRL agonists) was done using Student T-test. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A p-value < 0.05 was considered significant.

Study Objectives:

- Toxicity was assessed by CTCAE version 22.
- The primary end point is evaluating overall survival (OS) and disease free survival (DFS).
- The Secondary end points are toxicity will be collected from files or from review in clinical setting.

Overall survival (OS): defined as time from received hormonal treatment till death from any cause or from the date of the last follow-up visit.

Disease free survival (DFS): defined as the time from received hormonal treatment to the first appearance of one of the following: recurrence of invasive breast cancer (local, regional, or distant), invasive contralateral breast cancer, or death.

RESULTS

Table 1: total data collection

Total NO.	Groups

	Tamoxifen		Tamoxifen+ LHRH agonists		Total	
	N	%	N	%	N	%
Total	173	60.7	112	39.3	285	100.00

Table 2: age

Age	Groups					
	Tamoxifen			Tamoxifen+ LHRH agonists		
Range	21	-	49	20	-	48
Mean ±SD	37.480	±	5.928	37.098	±	4.589
Median	38			38		

Table 3: toxicity analysis

	Tamoxifen only	Tamoxifen +LHRH agonist	
No toxicity (%)	151 53%	110 38.59%	262 91.6%
Hot Flushes (%)	0 0%	9 3.15%	9 3.15%
Vaginal Bleeding (%)	12 4.2%	1 0.35%	13 4.6%
Endometrial Hyperplasia (%)	1 0.35%	0 0.0%	1 0.35%
Osteopania (%)	0 0.0	1 0.35%	0.35 %
Total (%)	173 100.0%	112 100.0%	285 100.0%

Table 4: overall survival and its relation to the prognostic factors

		OS (months)			95% Confidence Interval		P-value
		No.	Median survival (months)	Cumulative survival at 36 months (%)	Lower Bound	Upper Bound	
Age	**≤35yrs**	**91**	42.00	71.5%	40.065	43.935	0.239
	36-39yrs	81	48.00	80.4%	-	-	
	≥40yrs	113	52.00	77.8%	-	-	
T stage	T1	57	42	72.4%	154	154	0.525
	T2	154	49	77.8%	39.192	58.808	
	T3	65	48	75.4%	38.168	57.832	
	T4	9	-	-	-	-	
N stage	N0	73	-	83.1%	-	-	0.026
	N1	89	-	79.0%	-	-	
	N2	65	49.00	74.2%	-	-	
	N3	58	40.00	66.6%	36.120	43.880	
Surgery	MRM	151	48.00	74.1%	-	-	0.263
	BCS	134	49.00	79.5%	39.175	58.825	
Chemo	No	9	-	-	-	-	0.047
	Yes	276	-	75.4%	-	-	
Radio	No	6	-	-	-	-	0.173
	Yes	279	-	75.9%	-	-	
Her2	No	263	49.000	79.0%	40.700	57.300	0.027
	Yes	22	39.000	55.8%	32.808	45.192	

Table 5: disease free survival and its relation to the prognostic factors

	DFS (months)			95% Confidence Interval		P-value
	No.	Median relapse	Cumulative at 36 months (%)	Lower Bound	Upper Bound	

			(months)				
Age	**≤35yrs**	**91**	42.000	54.8%	36.171	47.829	0.717
	36-39yrs	81	-	59.9%	-	.-	
	≥40yrs	113	-	61.2%	-	-	
T stage	T1	57	42.000	61.0%	35.239	48.761	0.547
	T2	154	39.000	56.7%	.	.	
	T3	65	42.000	58.9%	34.526	49.474	
	T4	9	.	-	.	.	
N stage	N0	73	.	67.1%	.	.	0.011
	N1	89	.	61.9%	.	.	
	N2	65	39.000	59.0%	33.612	44.388	
	N3	58	33.000	41.1%	22.215	43.785	
Surgery	MRM	151	42.000	59.0%	37.738	46.262	0.472
	BCS	134	.	58.1%	.	.	
Chemo	No	9	-	-	-	-	0**.012**
	Yes	276	-	57.2%	-	-	
Radio	No	6	-	-	-	-	0.064
	Yes	279	-	57.8%	-	-	
Her2	No	263	43.000	60.1%		.	0.095
	Yes	22	30.000	45.5%	11.690	48.310	

Table 6: DFS with age group (≤35 years)

	Median				P-value
	Estimate	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Tamoxifen only	25.000	5.340	14.533	35.467	
Tamoxifen +LHRH agonist	42.000	1.751	38.568	45.432	**0. .052**
Overall	42.000	2.974	36.171	47.829	

DISCUSSION

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women [(2)]**.**We estimated the individual patient's disease free survival and overall survival by calculating a composite measure of DFS and OS from conventional clinicopathologic factors, including age, nodal status, tumor size and. HER-2neu.The **SOFT Trial (2015)** (Suppression of Ovarian Function Trial) reported no significant difference in overall survival (OS) at 5 years was 96.7% among patients assigned to tamoxifen plus ovarian suppression and 95.1% among those assigned to tamoxifen alone (P = 0.13).Similar to this study reported no statistical significant difference in overall survival at 2 years was 89.8% among those assigned to tamoxifen alone and 85.9 % among patients assigned to tamoxifen plus ovarian suppression (P=0.15 not significant). In our retrospective analysis there was no statistical significant difference in the primary endpoint of disease free survival (DFS) between group I received tamoxifen and group II received tamoxifen plus ovarian suppression (DFS at 2 years, 65.3% vs. 75.0%) with **(***P* value=0.838 not significant).Our study consistent with the findings of soft primary analysis which showed no statistical significant difference in the primary endpoint of DFS between the patients who received tamoxifen and those who received tamoxifen plus ovarian suppression (5-year DFS, 84.7% vs. 86.6%), (95%CI: 0.66-0.04) **(**p=0.10 not significant). But, patients in SOFT trail have longer overall survival and DFS due to low stage and low grade, about 65.5 % of patients with tumor size ≤ 2cm and negative lymph node was 65.1% in SOFT Trail but in our study patients have higher stage About of, 80% of patients with tumor size ≥ 2cm and positive lymph node were 74.3%.The majority of our patients received tamoxifen alone and tamoxifen plus ovarian suppression showed no statistical significant difference regarding toxicity, treatment-related adverse events were mild and manageable. Patients who received TAM and ovarian suppression were more affected by hot flushes than patients received TAM alone (3.1% vs. 0.0%).In Soft Trail used similar regimens and reported similar toxicities with higher severity according to hot flushes for patients who received TAM and ovarian suppression vs. patients received tamoxifen alone (93.4% vs. 79.8%).

There was no statistical significant difference in OS regarding to tumor size, T1 was 67.9% among those assigned to tamoxifen alone and 75.9%among patients assigned to tamoxifen plus ovarian suppression (P=0.425)**.** T2 was 76.0% among those assigned to tamoxifen alone and 72.4% among patients assigned to tamoxifen plus ovarian suppression (P=0.246).Also, T3 was 81.0%among those assigned to tamoxifen alone and 65.2%among patients assigned to tamoxifen plus ovarian suppression (P=0.069).and finally T4 showed no statistics are reported because all cases are censored.In our study patients with lymph node infiltration (**N1)** achieved significantly longer OS was 88.9 % assigned to tamoxifen alone vs 71.4% for those assigned to tamoxifen plus ovarian suppression **(**P=0.019, significant**).**we did not have any explanation for this finding.The additional benefit of chemotherapy for premenopausal patients with endocrine-responsive breast cancer who received combined endocrine treatment with OFS and tamoxifen (or an aromatase inhibitor) remained an open question that prospective randomized clinical trials have been unsuccessful in answering, as diverging opinions regarding its efficacy result in some physicians recommending it while, others did not.In our study there was no statistical significant difference between patients who received TAM vs. patient received TAM and LHRH agonist, after chemotherapy completion regarding DFS (p=0.61 not significant).) And OS (P=0.081 not significant). These results are similar to those of **Francis *et al.*** [(7)] who showed that overall survival at 5 years in the chemotherapy cohort was 94.5% (95% CI, 92.0 to 96.2) among patients assigned to tamoxifen plus ovarian suppression, as compared to 90.9% (95% CI, 87.9 to 93.2) among those assigned to tamoxifen alone. In our study there was no statistical significant difference between patients who received TAM vs. patient received TAM and LHRH agonist, after radiotherapy completion regarding DFS (p=0.956 not significant) and **OS** (P=0.208 not significant). In the SOFT trial, the most striking difference was observed in women younger than 35: among the 233 patients included in the primary analysis, the rate of freedom from breast cancer at five years was 67.7% for patients treated with tamoxifen alone, 78.9% for those treated with tamoxifen plus OFS The data on overall survival is not yet mature and longer follow-up is warranted [(7)]**.**In our retrospective study, a total of 75 women younger than 35 years of age, Among these women, DFS was 40.7%for patients assigned to tamoxifen and tamoxifen plus OFS was 62.5% (P=0.052, not significant***)*** and OS was 63.0%for patients assigned to tamoxifen, 73.4%for tamoxifen and tamoxifen plus OFS (P=0. 495, not significant) and there was not related to breast cancer, freedom in our study. In our study, there was no statistical difference in DFS &OS of patients with Her-2neu positive who assigned to tamoxifen alone, and those assigned to tamoxifen plus ovarian suppression (P=0.770) and P=0.676 respectively**.** That can be explained by number of patients with Her-2neu positive were 22 and all patients received trastuzumab (Herceptin) as reported from files. Finally the differences between our study and other trail regarding longer OS and DFS related to higher number of patient in other trail then in our study and longer follow up.

CONCLUSION

We concluded that adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall population of premenopausal women in this study (P=0.15 not significant). Any benefit from ovarian suppression must be weighed against the adverse effects. Adding ovarian suppression to tamoxifen resulted in increased adverse events — most notably, menopausal symptoms. Our patients received tamoxifen alone and tamoxifen plus ovarian suppression show no *statistical significant difference regarding* toxicity, treatment-related adverse events were mild and manageable. Patients who received TAM and ovarian suppression were more affected by hot flushes than patients received TAM alone (3.1% vs. 0.0%). Progress has been made in our understanding of the role of adjuvant ovarian function suppression in premenopausal women with early-stage breast cancer, but many questions remain. Numerous prior studies have convincingly shown a clear benefit from adjuvant endocrine therapy. For women with low-risk disease, the addition of ovarian suppression to tamoxifen did not a substantial benefit.

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